amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_8$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_8$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_8$;

R_8 represents a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle; and

n and m are independently for each occurrence zero or an integer in the range of 1 to 6.

25. (Amended) The method of claim 1, wherein the [patient] individual is hypotensive.

33. (Amended) The method of any of claims 1-6, wherein the *ptc* [therapeutc] therapeutic agonizes the activity of cAMP phosphodiesterase.

34. (Amended) A therapeutic preparation [of] comprising a *hedgehog* polypeptide and a small molecule antagonist of *patched*, [which *patched* antagonist inhibits PKC with a K_i greater than 1 μM and is] provided in a pharmaceutically acceptable carrier and in [an] amounts sufficient to provide protection against neuronal cell death under ischemic and/or hypoxic conditions.

REMARKS

Claims 1-37 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants have amended the specification as suggested by the Examiner. Although Applicants submit that hyperlinks are ordinarily proper, the hyperlink objected to by the Examiner has expired. Accordingly, Applicants have deleted this reference.

Claims 1-37 are rejected under 35 U.S.C. § 101 because the claimed invention allegedly lacks patentable utility. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants respectfully direct the Examiner's attention to MPEP 2107.01, which discusses the procedural requirements for a rejection on the basis of lack of utility. As entry III.A. indicates, an asserted utility, as is the case in the present application, creates a presumption of utility. "As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement... unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." (emphasis in original) *In re Langer*, 183 USPQ 288 at 297 (CCPA 1974). As indicated in entry III.B., an assertion is credible "unless (A) the logic underlying the assumption is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion." Although the Office Action asserts that there is "no indication that such models would be predictive of similar effect to the intended host", the Office Action does not establish the flawed logic or inconsistencies necessary to set forth a *prima facie* case of lack of utility.

Applicants also point out that the rat models were used as the best available animal stroke model. Indeed, experimentalists should not be expected to wait for rats to naturally suffer from strokes in order to demonstrate utility of a potential stroke therapy. The Federal Circuit is responsive to this concern: "If applicants were required to wait until an animal naturally developed this specific [condition] before testing the effectiveness of a compound... there would be no effective way to test compounds *in vivo* on a large scale." *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Applicants submit that this concern applies equally to the experiments performed by Applicants as described in the present specification. Moreover, the Examiner has provided no evidence suggesting that the animal models used are inadequate to test effectiveness for stroke therapies. Applicants provide herewith as Exhibit A a couple of abstracts indicating that the MCAO model is widely accepted as a model for stroke. Since the damage caused by stroke is largely due to insufficient oxygen delivery to the brain, the manner in which oxygen deficiency is induced should be largely irrelevant to the success of a compound in limiting damage caused by the oxygen deficiency. For all of these reasons, one of skill in the art would find that Applicants have demonstrated utility for the claimed invention, even had a *prima facie* case of lack of utility been established.

The Office Action also appears to question whether the example of Shh is sufficient to indicate that the broader class of ptc therapeutics would be effective in the claimed methods. Applicants respectfully point out that one of skill in the art would readily expect that when a *hedgehog* protein (such as Shh) shows therapeutic efficacy, ptc therapeutics, defined on page 13, lines 15-18, of the specification as agents which mimic the effect of *hedgehog* proteins on *patched* signalling, would also be effective therapeutic agents. Accordingly, Applicants submit that one of skill in the art would expect the broad class of ptc therapeutics to have utility.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended the present claims to remove the limitation on which this rejection was based, solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-37 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

In claim 1, Applicants have replaced the term 'epoxic' with 'hypoxic', which appears in the specification on page 20, line 6, and original claim 34, for example. Applicants submit that the term 'ischemic' is not indefinite. The meaning of the term is elaborated on page 2, from lines 6-19, and is a common medical term whose meaning is well known to those of skill in the art. Applicants have removed the term PKC solely to expedite prosecution of the remaining claims, but submit that the term *ptc* therapeutic is defined on page 13, lines 15-17, and the term '*ptc* therapeutic' is used throughout the specification. Because '*ptc* therapeutic' does not refer to or rely on *patched* for structural definition, Applicants submit that amending this term to *patched* therapeutic would only be *more* unclear, because the term '*patched* therapeutic' is not used in the specification, not defined in the specification, and is not well known in the art. Applicants have

also amended claim 1 to clarify the function of the *ptc* therapeutic in the method. Accordingly, Applicants request that the term *ptc* therapeutic be permitted to stand.

Applicants further submit that the term 'cerebral infarct volume' is not indefinite. This term is used several times throughout the specification, and, as indicated by representative literature abstracts, is understood in the art and can be measured by one of skill in the art using well known techniques. The basis of the Examiner's statement that the phrase 'cerebral infarct volume' is inconsistent with the preamble recitation of neuronal cells is unclear to Applicants. Applicants refer again to the specification on page 2, lines 6-19, which explains how ischemia and infarctions are related. Accordingly, Applicants submit that 'cerebral infarct volume' is both clear and consistent with the rest of the claim.

Applicants have amended claims 2-6 as suggested by the Examiner to remove the redundant recitation of 'therapeutic'.

Applicants point out that, although claims 2 and 3 may be similar in scope, they are not identical in scope, and thus neither claim is properly rejected as indefinite or for double patenting reasons. For example, claim 2 might be construed to cover treatment of mild ischemic damage that does not result in a clinical diagnosis of an infarction, and would thus not be covered by claim 3. Applicants submit that inclusion of claims of differing scope is proper.

Applicants submit that it is not unclear how a *ptc* therapeutic would mimic *hedgehog*-mediated *patched* signal transduction. The specification on page 5, lines 12-18, gives examples of how a *ptc* therapeutic might mimic *hedgehog*-mediated *patched* signal transduction. *Hedgehog*-mediated *patched* signal transduction was well known in the art at the time of filing of the present application, and thus the specification combined with the level of skill in the art support Applicants' contention that one of skill in the art would not find this phrase indefinite.

Applicants respectfully point out that the specification defines the term "small organic molecule" on page 5, lines 19-20. Nevertheless, to expedite prosecution of the pending claims, Applicants have amended claims 8 and 13 to include a portion of this definition.

Applicants submit that the manner in which a *ptc* therapeutic interacts with or affects a protein in the *hedgehog* pathway can be determined using standard biochemical techniques.

Because most human individuals exhibit an extremely high degree of homology between their proteins, one of skill in the art would expect that the mode of action elucidated *in vitro* would be consistent with its mode of action *in vivo*. Thus, determining whether a particular method falls within the scope of the claim would not require investigating the molecular interactions within a particular patient. Accordingly, Applicants submit that claims 11-13 are clear as written.

Claim 16 has been amended by Applicants as suggested by the Examiner to remove the terms 'can' and 'stability permit', and the phrases introduced by 'such as'. Applicants submit that the claim as amended is clear and definite. Applicants submit that the term 'lower' is well understood in the art and requires no further elaboration. Applicants have amended the definition of R_1 and R_2 to clarify the substituents from which these groups may be selected, and have moved the reference to 'valence' to apply to all the subsituents.

Applicants submit that the term KT5720 is not indefinite, as this compound is commonly known by this name. A search on PubMed for KT5720 returned 225 hits, underscoring the common usage of this term. See, for example, http://www.fermentek.co.il/products1.html, which sells KT5720 as a potent specific PKA inhibitor. Accordingly, Applicants submit that the term 'KT5720' clearly and distinctly refers to a particular compound, and is not indefinite.

Each of claims 3-6 uses the phrase 'a patient'. Applicants submit that the term 'the patient', as used in claim 22 which depends on claims 3-6, thus has proper antecedent basis.

The recitation of "the mammal" in claim 24 properly refers back to "a mammal" in claim 2, from which claim 24 depends. Applicants submits that the Office Actions reference to "the individual" is incorrect. Applicants have, however, amended claim 25 to properly refer back to the 'individual' as recited in claim 1, rather than the 'patient'.

Claims 1-16 and 18-37 are rejected under 35 U.S.C. 102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. 103(a) as obvious over Maiese et al. or Satoh et al. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended the pending claims to recite administration of a therapeutic regimen comprising administering a *hedgehog* polypeptide and administering a *ptc* therapeutic. None of the cited references teach or suggest administration of *hedgehog* polypeptide as part of a

therapeutic regimen for treating any of the conditions recited in the claims. Accordingly, Applicants assert that one of ordinary skill in the art would not have been motivated to arrive at the present invention based on Maiese et al. and Satoh et al., taken individually or in combination, and thus these references do not render the claimed invention obvious. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 1-16 and 18-37 are rejected under 35 U.S.C. 102(e) as being anticipated by or obvious over Andrulis et al., U.S. Patent No. 5,643,915. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended the pending claims to recite administration of a therapeutic regimen comprising administering a *hedgehog* polypeptide and administering a *ptc* therapeutic. None of the cited references teach or suggest administration of *hedgehog* polypeptide as part of a therapeutic regimen for treating any of the conditions recited in the claims. Accordingly, Applicants assert that one of ordinary skill in the art would not have been motivated to arrive at the present invention based on the art of record, taken individually or in combination, and thus these references do not render the claimed invention obvious. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 17 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over any of Maiese or Satoh or Andrulis in view of Ikegaki et al. (5,747,507). Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

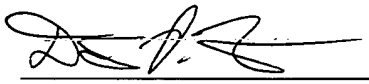
Applicants have amended the pending claims to recite administration of a therapeutic regimen comprising administering a *hedgehog* polypeptide and administering a *ptc* therapeutic. None of the cited references teach or suggest administration of *hedgehog* polypeptide as part of a therapeutic regimen for treating any of the conditions recited in the claims. Accordingly, Applicants assert that one of ordinary skill in the art would not have been motivated to arrive at the present invention based on Maiese et al., Andrulis et al., Ikegaki et al., and Satoh et al., taken individually or in combination, and thus these references do not render the claimed invention obvious. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this Reply, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,



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